ImmunoTools *special* Award 2025

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Mechano-immunomodulatory strategies for bone fracture repair

Introduction

Mechano-immunology, the study of how mechanical forces influence immune responses, is an emerging and transformative field at the crossroads of immunology, biomechanics, and regenerative medicine. Traditionally, our understanding of immune cell behaviour has focused on biochemical signals. However, growing evidence reveals that immune cells, particularly macrophages, are also highly responsive to mechanical cues. This insight is especially relevant in the context of bone healing, where the mechanical environment plays a dynamic and critical role in guiding the repair process.

Current clinical approaches to treat bone fractures, especially in osteoporotic patients, are aimed at the later stages of healing, such as bone formation and repair phases. As a result, these strategies often neglect the early immune response, an inflammatory phase that is crucial for initiating tissue regeneration. Macrophages are key players in this early stage, orchestrating the transition from a pro-inflammatory (M1) to a pro-regenerative (M2) phenotype. However, the extent to which mechanical strain modulates this switch remains poorly understood. This knowledge gap is particularly concerning in the case of osteoporosis, a chronic bone disease affecting over 200 million people worldwide. In osteoporotic patients, the early inflammatory response following a fracture is often impaired. Globally, an osteoporotic fracture occurs every 3 seconds, with the associated healthcare costs exceeding €36 billion annually in Europe alone. Alarmingly, 20% of patients over the age of 60 die within a year of suffering a major osteoporotic fracture, underscoring the urgent need for more effective early-stage therapeutic strategies.

Project outline

My research aims to provide a better understanding on how mechanical stimulation can affect macrophage phenotypes and establish an immune environment conducive to tissue repair. It comprises a 5-year project supported by Research Ireland FFP Award program. The work will

focus on establishing a dynamic 3D *in vitro* model that mimics the early fracture hematoma. Inthis model, human macrophages (differentiated from THP-1 cells or PBMCs) are embedded within a fibrin hydrogel and subjected to controlled cyclic compression using a custom- designed bioreactor. By applying physiologically relevant strain levels (1–5%), we aim to understand how mechanical signals influence macrophage phenotype, cytokine production, and their regenerative potential. The response of macrophages will be assessed using flow cytometry, cytokine analysis (ELISA), and functional assays to evaluate osteogenesis and angiogenesis using monoculture and co-culture models. Comparisons will be made between mechanically stimulated macrophages and those classically polarized via exposure to inflammatory or regenerative cytokines.

The novelty of this research lies in its mechanistic focus on immune–mechanical interactions, a dimension that has been largely ignored in tissue repair strategies. By identifying mechanical conditions that promote regenerative immune profiles, our work could lead to the development of mechanically informed therapeutics that leverage innate immunity to accelerate healing.

Application and visibility of ImmunoTools technology

ImmunoTools offers a range of products tailored to the needs of our project which can complement our experiments. Specifically, we are interested in **human IL-6** and **human IL-8 ELISA kits** which will be used to assess the polarisation of M1 and M2 macrophages, respectively. In addition, we are interested in the **rhVEGF-A/VEGF-165** and **rh TNF*α*** which will be used for supplements to initiate angiogenesis and osteogenesis, respectively.
We are committed to acknowledge ImmunoTools products and support in all relevant scientific journal article and conference presentations.

Expected outcome and impact

We anticipate that dynamic loading will modulate cytokine secretion patterns, revealing time- and intensity-dependent shifts in macrophage phenotype. These insights could inform biomaterial design and rehabilitation protocols that harness immune modulation for enhanced tissue repair. Conclusions from this research can provide new knowledge on accelerating bone healing and holds the potential to significantly improve the quality of life for the growing aging population affected by osteoporosis, while also offering hope for younger individuals suffering from rare or secondary forms of the disease.

References

1. Petrousek SR, Kronemberger GS, O'Brien G, Hughes C, O'Rourke SA, Lally C, Dunne A, Kelly DJ, Hoey DA. Mechano-immunomodulation of macrophages influences the regenerative environment of fracture healing through the regulation of angiogenesis and osteogenesis. Acta Biomater. 2025 Jun 15;200:187-201. doi: 10.1016/j.actbio.2025.05.045. Epub 2025 May 21. PMID: 40409508.
2. Petrousek SR, Kronemberger GS, O'Rourke SA, Shanley LC, Dunne A, Kelly DJ, Hoey DA. Human macrophage polarisation and regulation of angiogenesis and osteogenesis is dependent on culture extracellular matrix and dimensionality. Biochem Biophys Res Commun. 2024 Nov 26;735:150835. doi: 10.1016/j.bbrc.2024.150835. Epub 2024 Oct 16. PMID: 39426136.

ImmunoTools *special* AWARD for **Matilde Tanganelli**

includes 10 reagents

human ELISA-Kits: human IL-6, human IL-8

Recombinant human cytokines: rhVEGF-A/VEGF-165 and rh TNFα

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